HDAT9700

Interrupted time series analysis

Online tutorial

CENTRE FOR
BIG DATA RESEARCH
IN HEALTH

Overview

1. What is interrupted time series (ITS) analysis, why do we need it, and when to use it?

2. Performing ITS analysis using segmented regression and ARIMA

What is interrupted time series analysis?

Interrupted times series analysis uses **time series data to answer causal questions**

- Ideal for evaluating population-level policies or interventions

- One of the strongest study designs if an RCT is not feasible

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Why is interrupted time series analysis needed?

Population-level policies and regulations cannot easily be evaluated by randomised trials and are often implemented with a limited evidence base supporting their efficacy.

But…

Once implemented, did these interventions have the intended impact on health outcomes?

Did they have any *unintended* consequences?

How can we find out, given that everyone is exposed to the intervention?

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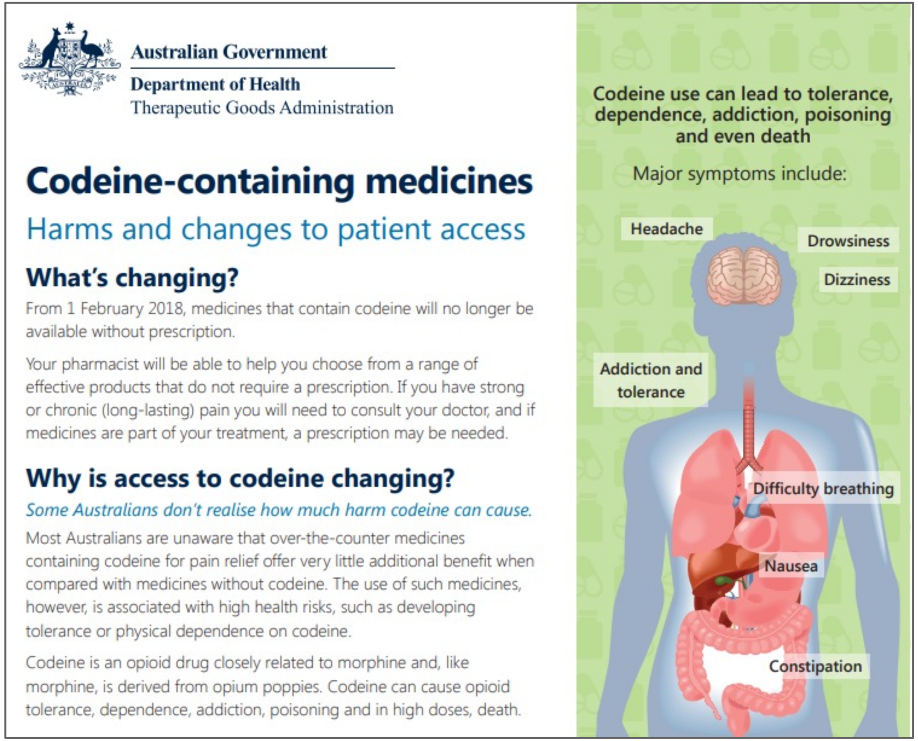
Example – codeine rescheduling in Australia

In February 2018, the Therapeutic Goods Administrative rescheduled codeine-containing products from OTC to prescription-only.

1. **What are the expected, positive outcomes of this intervention?**
2. **What are the potential negative outcomes?**
3. **Which outcomes can be measured using administrative data?**


Australian Government
Department of Health
Therapeutic Goods Administration

Codeine-containing medicines

Harms and changes to patient access

What's changing?

From 1 February 2018, medicines that contain codeine will no longer be available without prescription.

Your pharmacist will be able to help you choose from a range of effective products that do not require a prescription. If you have strong or chronic (long-lasting) pain you will need to consult your doctor, and if medicines are part of your treatment, a prescription may be needed.

Why is access to codeine changing?

Some Australians don't realise how much harm codeine can cause.

Most Australians are unaware that over-the-counter medicines containing codeine for pain relief offer very little additional benefit when compared with medicines without codeine. The use of such medicines, however, is associated with high health risks, such as developing tolerance or physical dependence on codeine.

Codeine is an opioid drug closely related to morphine and, like morphine, is derived from opium poppies. Codeine can cause opioid tolerance, dependence, addiction, poisoning and in high doses, death.

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Example – codeine rescheduling in Australia

Desired positive outcomes

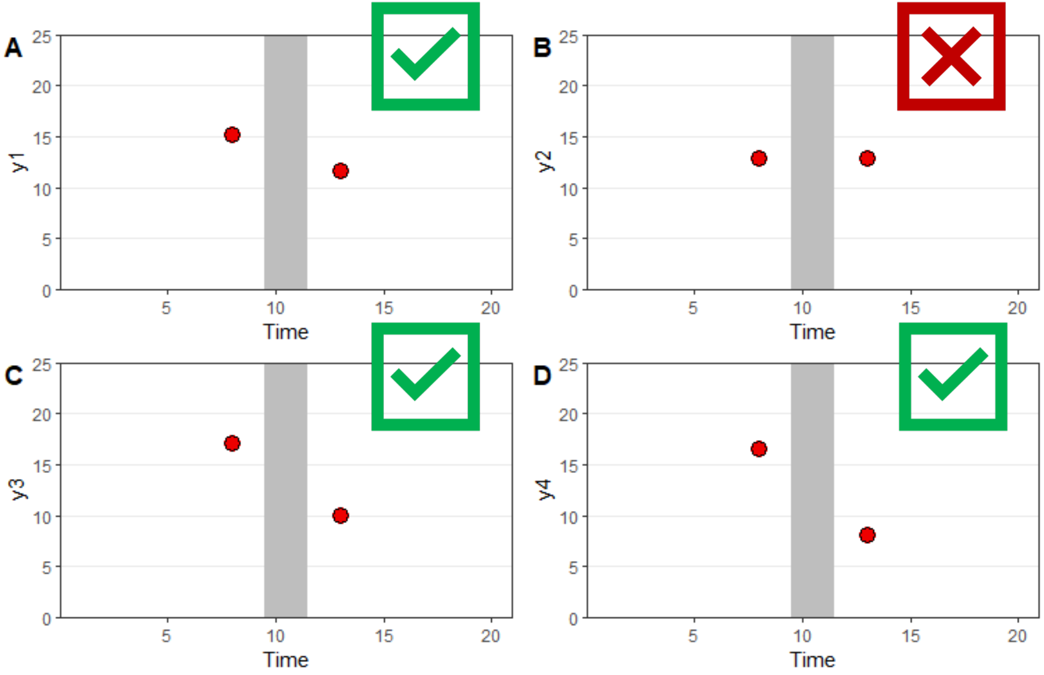
- Reduction in codeine dependence
- Reduction in inappropriate use of codeine
- Reduction in codeine overdose/poisonings
- Better pain management

Potential negative outcomes

- Increased medical costs (due to GP visits)
- Increased demand on healthcare system
- Increased use of strong (or other inappropriate) opioids
- Poorer pain relief

What about a before and after design?

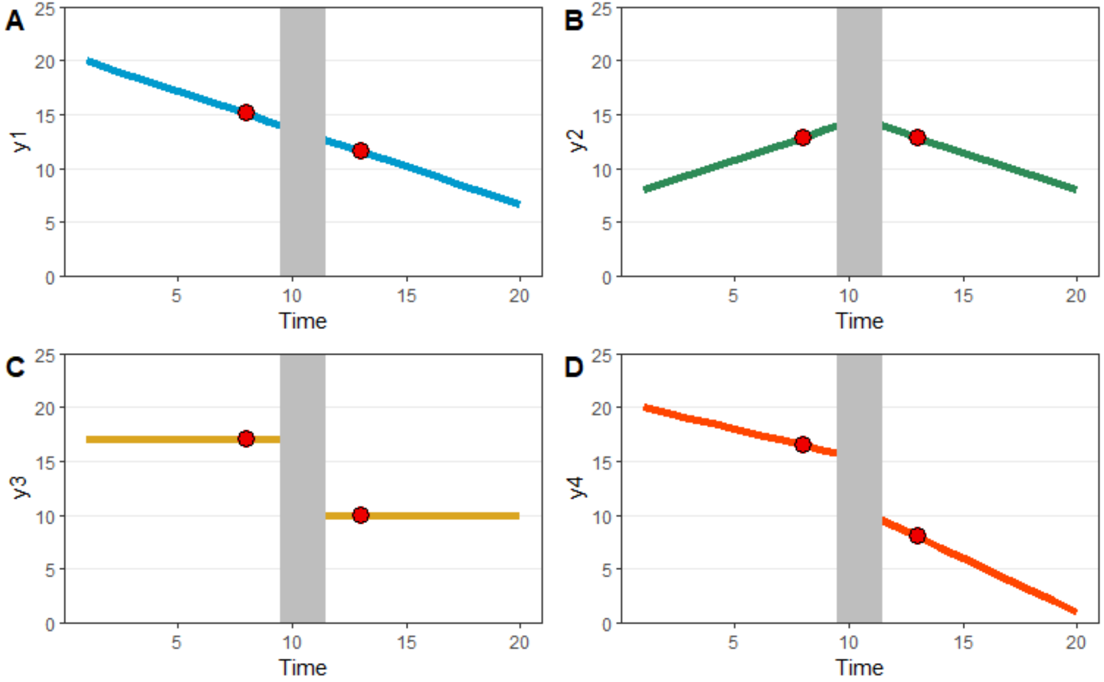
Comparing the red dots before-and-after the intervention (in grey), was there a reduction in the outcome *y*?



What about a before and after design?

Here's what it looks like if we plot the outcome over time (i.e. time series).

Is your conclusion the same?

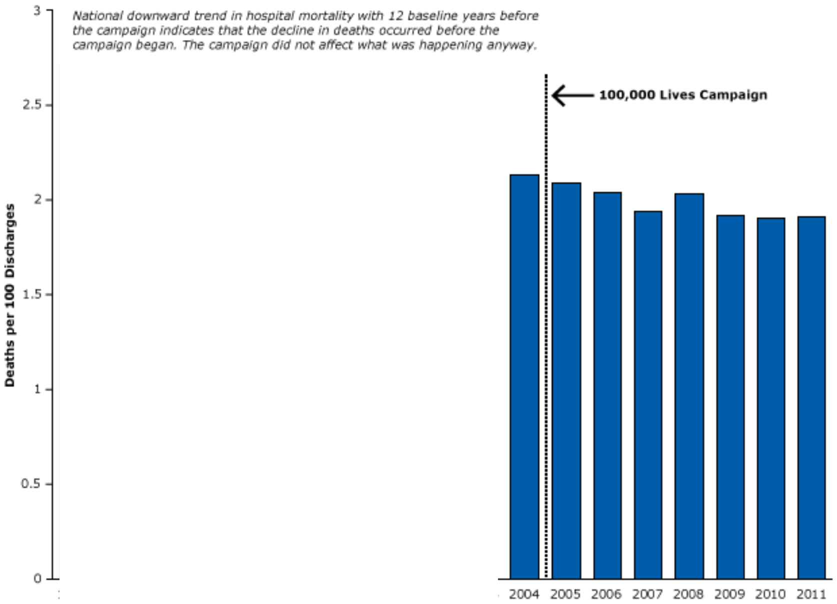


What about a before and after design?


Campaign against hospital mistakes says 122,000 lives saved

A campaign to reduce lethal errors and unnecessary deaths in U.S. hospitals has saved an estimated 122,300 lives in the last 18 months, the campaign's leader said Wednesday. . . . "We in health care have never seen or experienced anything like this," said Dr. Dennis O'Leary, president of the Joint Commission on Accreditation of Healthcare Organizations.

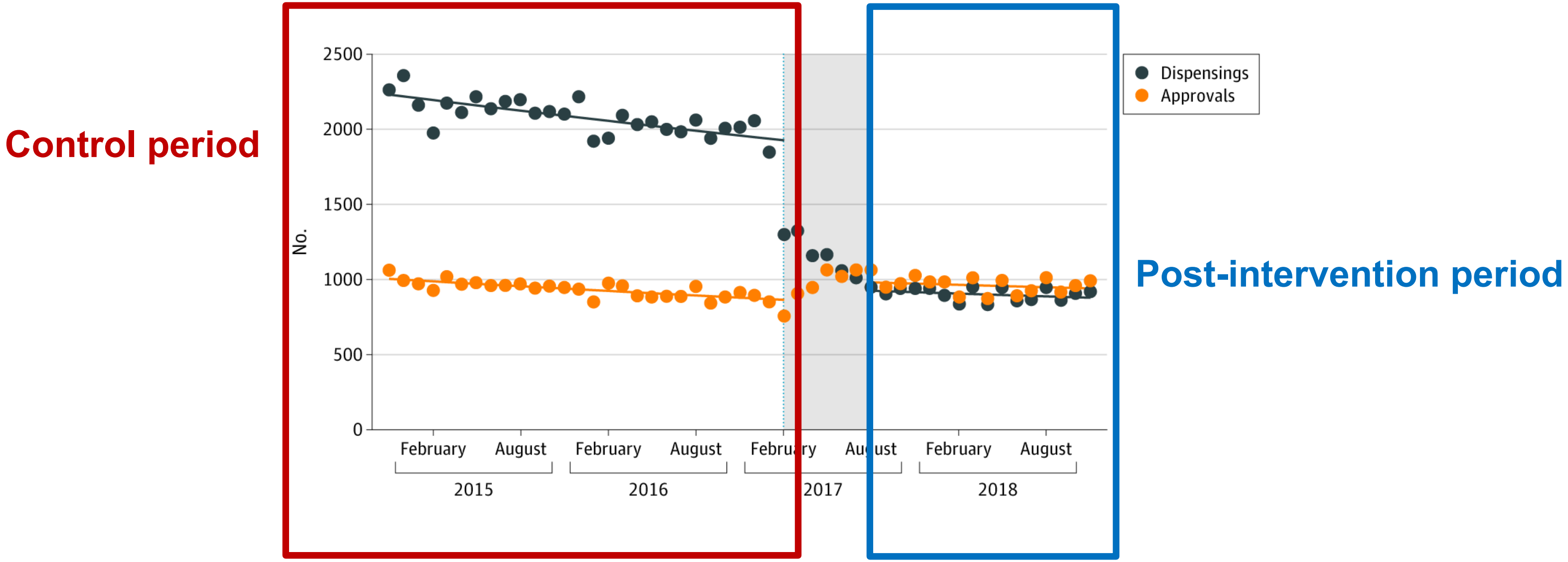
(Excerpted from www.foxnews.com/story/2006/06/14/campaign-against-hospital-mistakes-says-122000-lives-saved-in-18-months/.)



Soumerai et al. *Prev Chronic Dis* 2015;12:150187.
DOI: http://dx.doi.org/10.5888/pcd12.150187

ITS analysis takes advantage of the natural experiment occurring when an intervention is implemented

Intervention: Subsidy changes for alprazolam



Source: Schaffer at al. *JAMA Network Open* 2019;2(9):e1911590.

What types of interventions can be evaluated?

Occurs at **well-defined point in time**, with clear “before” and “after” periods

- In some cases there may be a “transition” period, e.g. due to gradual roll-out of intervention

Affects a **large proportion of population** of interest

Intervention = Tax increases on tobacco products

Outcome = smoking prevalence in Australian capital cities

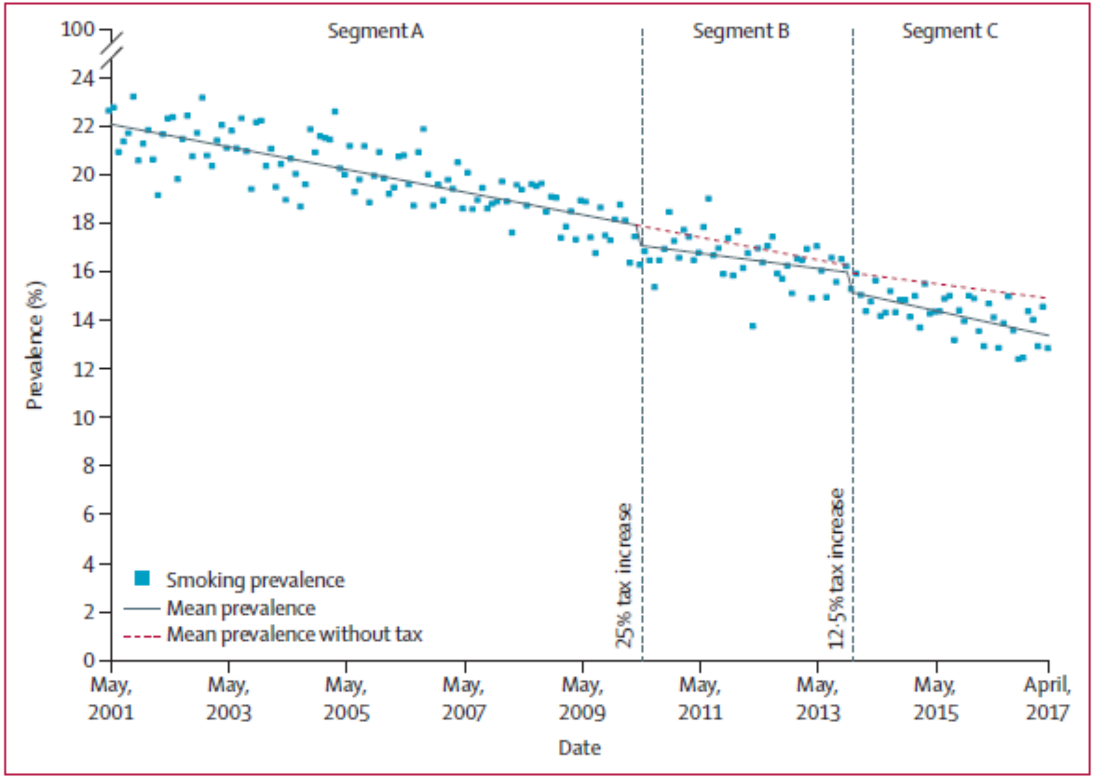


***Figure* 2: Month-level overall smoking prevalence in Australians aged 14 years and older residing in one of five capital cities between May, 2001, and April, 2017**

Data are as observed and predicted from an unadjusted interrupted time-series analysis. Red line shows predicted prevalence if taxes were not introduced.

Source: Wilkinson et al. *Lancet Public Health*. 2019;4:e618-27;

Intervention = Price decrease (2000) and increase (2008) on ready-to-drink alcoholic beverages ("alcopops")

Outcome = ED presentations for acute alcohol problems in young women

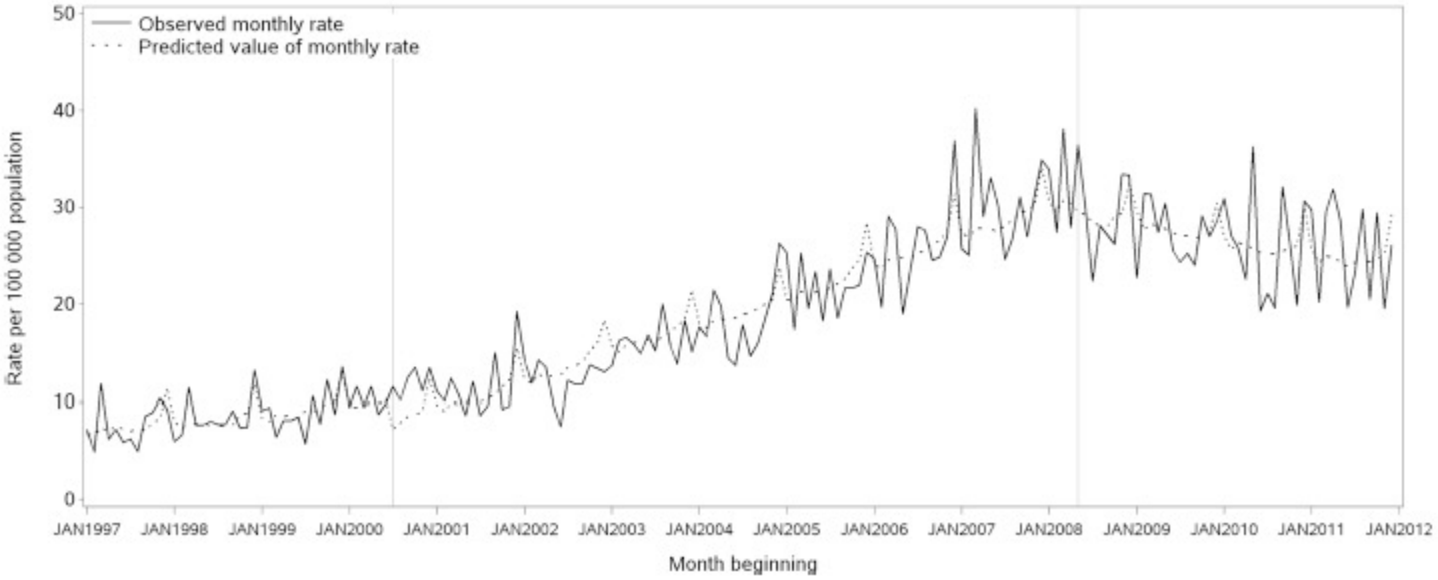
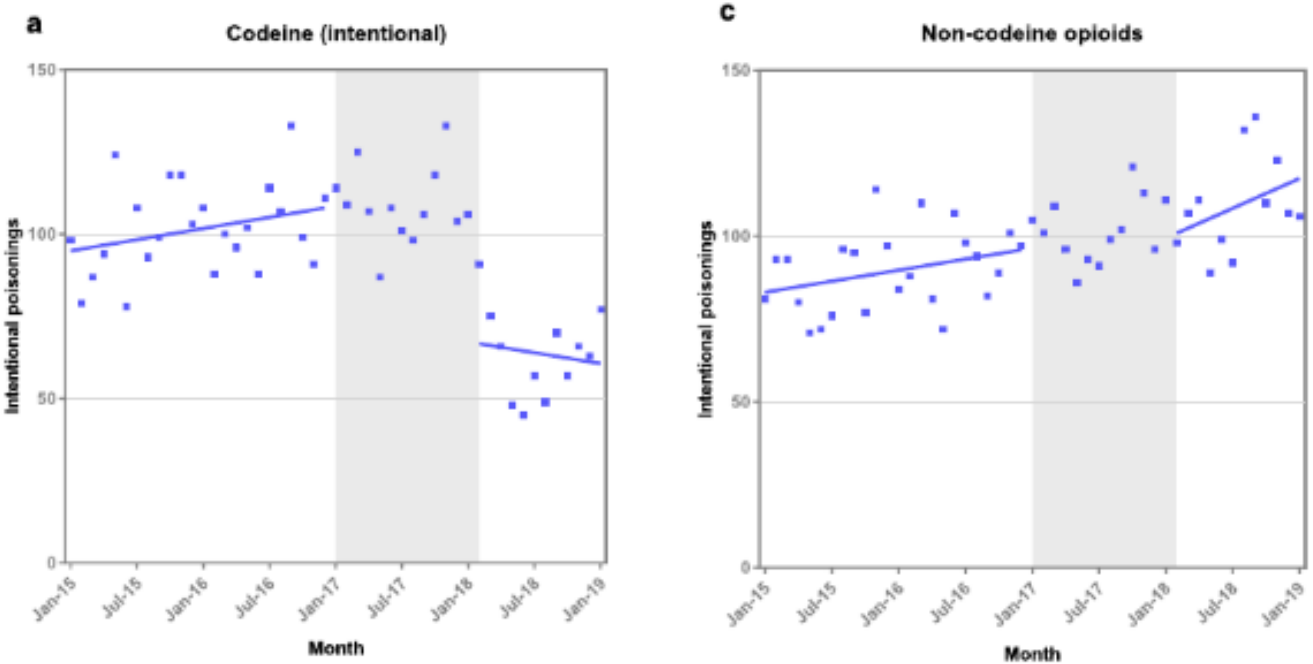


Figure 2 Total monthly rate of ED presentations for acute alcohol problems, females 18–24 years, 1997–2011.

Source: Gale et al. *BMC Public Health*. 2015;15:468.

Intervention = Rescheduling of codeine from over-the-counter to prescription-only
Outcome = Poisonings calls to the NSW Poisons Information Centre

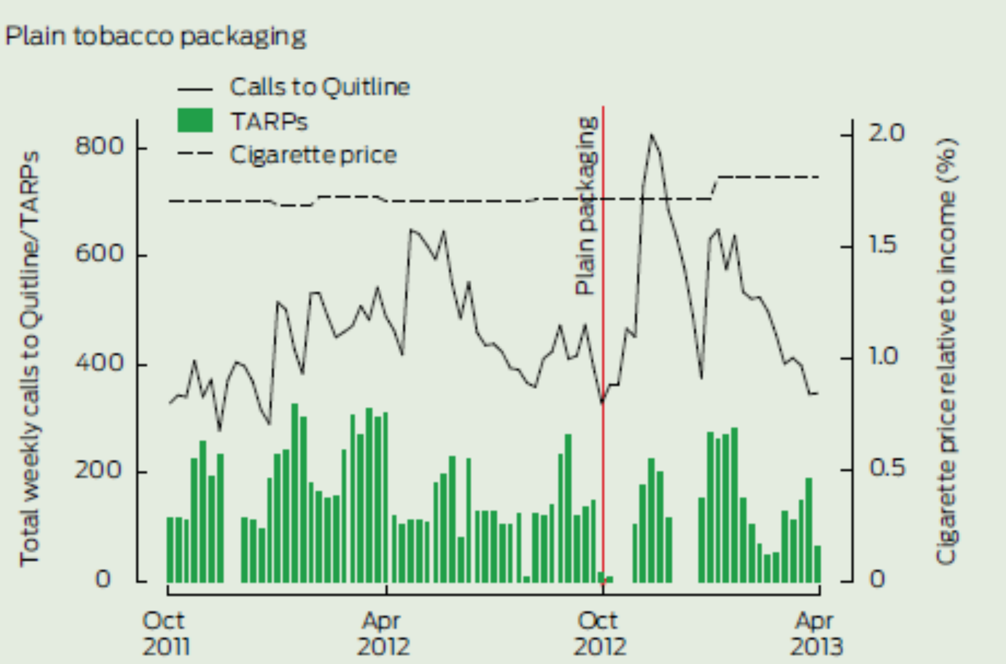


Source: Cairns et al. *Addiction.* 2020;115(3):451-459

Intervention = Plain tobacco packaging and graphic health warnings

Outcome = Calls to Quitline

2 Weekly calls to Quitline, target audience rating points (TARPs) and cigarette price relative to income, before and after the introduction of plain tobacco packaging and graphic health warnings



Young et al. *MJA* 2014;200(1):29.

See appendix: https://www.mja.com.au/journal/2014/200/1/association-between-tobacco-plain-packaging-and-quitline-calls-population-based

Main strengths and limitations of ITS

Strengths

- Takes into account pre-existing trends and patterns
- Selection bias and confounding are rare, assuming the underlying population is stable

Limitations

- Alternate explanations for the observed changes cannot definitively be ruled out, such as co-interventions at the same time
- It has limited ability to discern person-level predictors

Intervention impact – questions to consider

1. What is the shape of the impact?

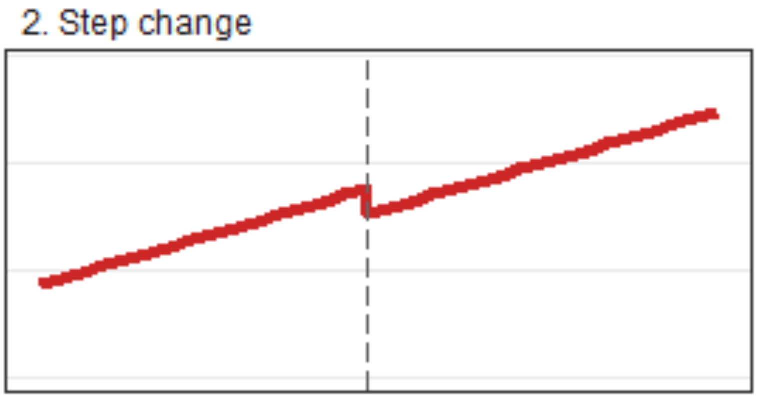
2. Was the impact immediate or delayed (lagged)?

3. Could a change have occurred in anticipation of the intervention?

4. Were there any other changes/intervention during the time period?

Step change (aka level shift)

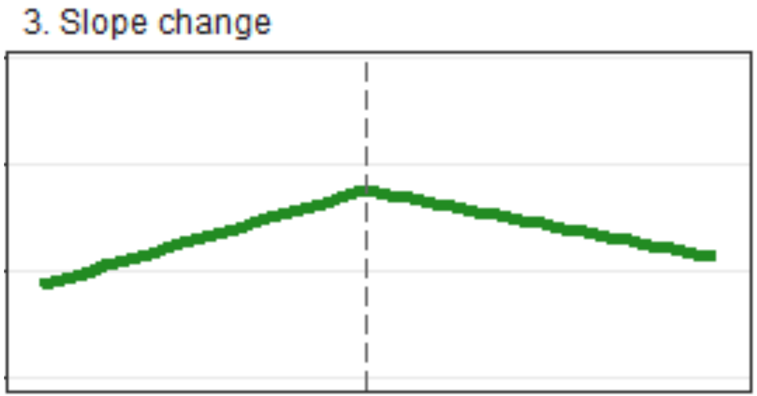
An **immediate** shift in the time series after the date of the intervention, either up or down, that is **sustained** for the duration of the study period.



Slope change (aka ramp)

An **immediate** change in the slope (i.e. the rate of change in the outcome over time) after the date of the intervention.

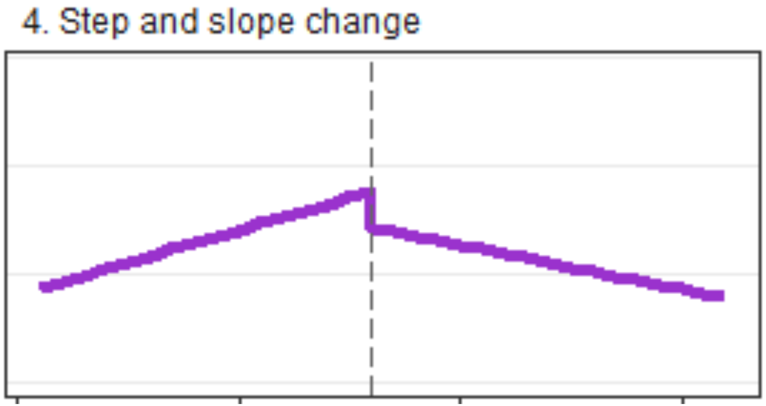
The slope may change sign (from positive to negative), or the rate of increase/decrease may get smaller or larger.



Step change AND slope change

It is not uncommon to see a step change AND slope change combined.

In this scenario, the time series immediately shift up or down, in addition to a change in the rate of change of the outcome.

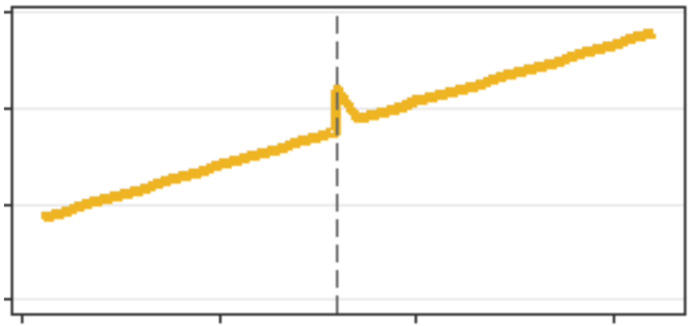


Pulse change

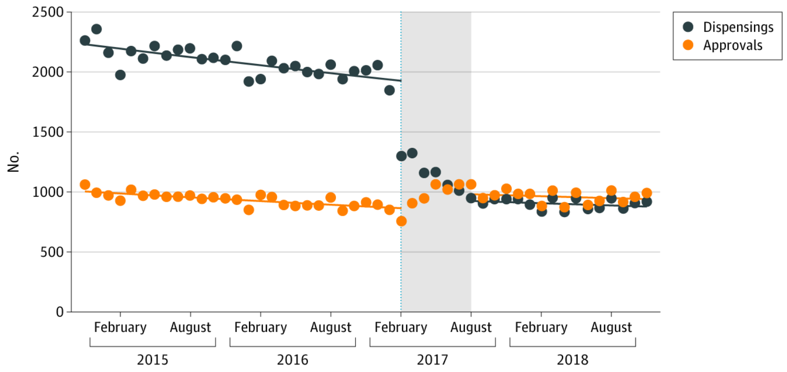
A **temporary** change in the outcome immediately after the date of the intervention, that reverts to pre-intervention levels.

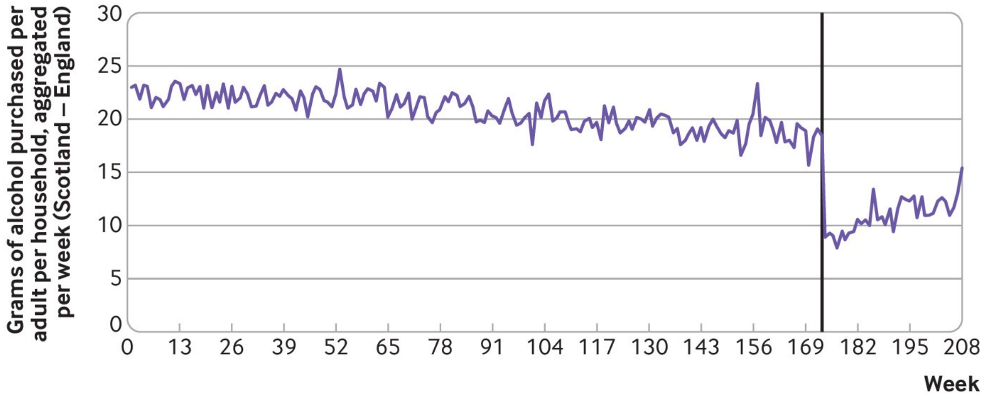
The duration of the pulse can vary from one time unit, to multiple.

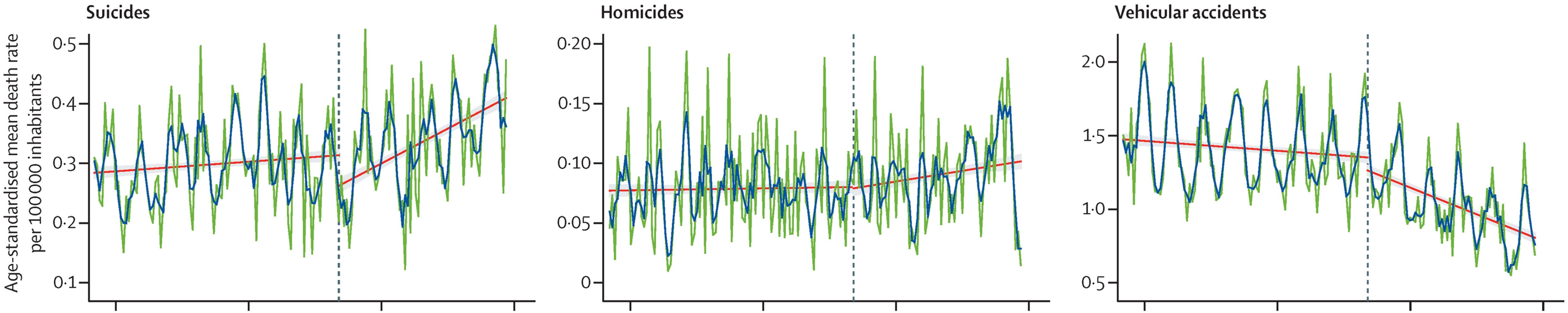
5. Pulse



Real life examples







Schaffer et al. *JAMA Network Open* 2019;2(9):e1911590; O'Donnell et al. *BMJ* 2019;366:l5274; Laliotis et al. *Lancet Public Health* 2016;1(2):e56.

Delayed impact

For some interventions and outcomes, the impact of the intervention may be delayed by one or multiple time points.

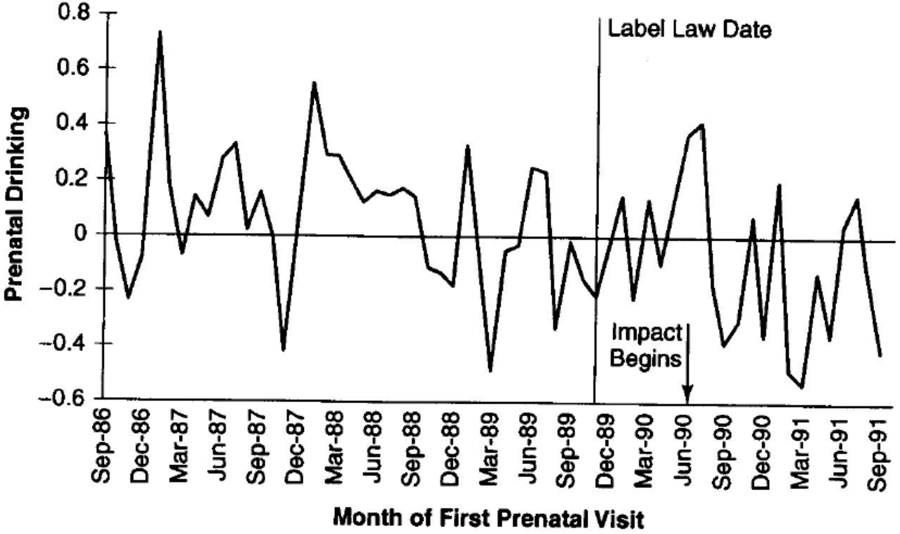


FIGURE 6.3 The effects of an alcohol warning label on prenatal drinking

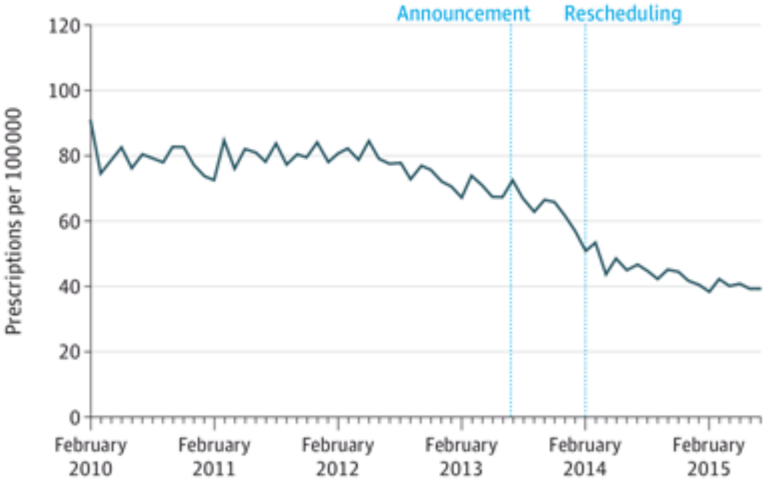
Shadish, Cook, Campbell. Experimental and quasi-experimental designs for generalized causal inference. 2002

What types of interventions can be evaluated?

Occurs at **well-defined point in time**, with clear “before” and “after” periods

Affects a **large proportion of population** of interest

Be aware that changes may occur in **anticipation** of the intervention if people know it is coming—this isn’t a dealbreaker but must be accounted for or excluded in your model



Example: Rescheduling of alprazolam to a “Controlled Drug” in Feb 2014—but the TGA announced this change in July 2013

Source: Schaffer et al. *JAMA Intern Med* 2016.

What determines the shape of the impact?

1. The nature of the intervention
2. The nature of the outcome
3. The frequency of the time series

The same intervention can lead to different types of impacts for different outcomes.

Is the impact immediate/delayed/gradual? Temporary/permanent?

Intervention	Outcome	Immediate or delayed?	Shape of impact?
Increase in tax on tobacco products	Sales of cigarettes	?	?
	Smoking rates	?	?
	Lung cancer diagnoses	?	?
Removal of high-strength opioids from the market	High-strength opioid sales	?	?
	Opioid dependence treatment	?	?

Negative control series

The **main limitation** of ITS analysis is potential confounding by other changes or interventions that may have occurred around the same time as the intervention of interest (*history bias*)

Adding a control series strengthens causal inference from ITS analysis.

A “**negative control**” is a group or outcome where you expect to see no impact (*more common in ITS analysis*).

A “**positive control**” is a group or outcome where you expect to see an impact (*less common in ITS analysis*).

How to interpret negative control series?

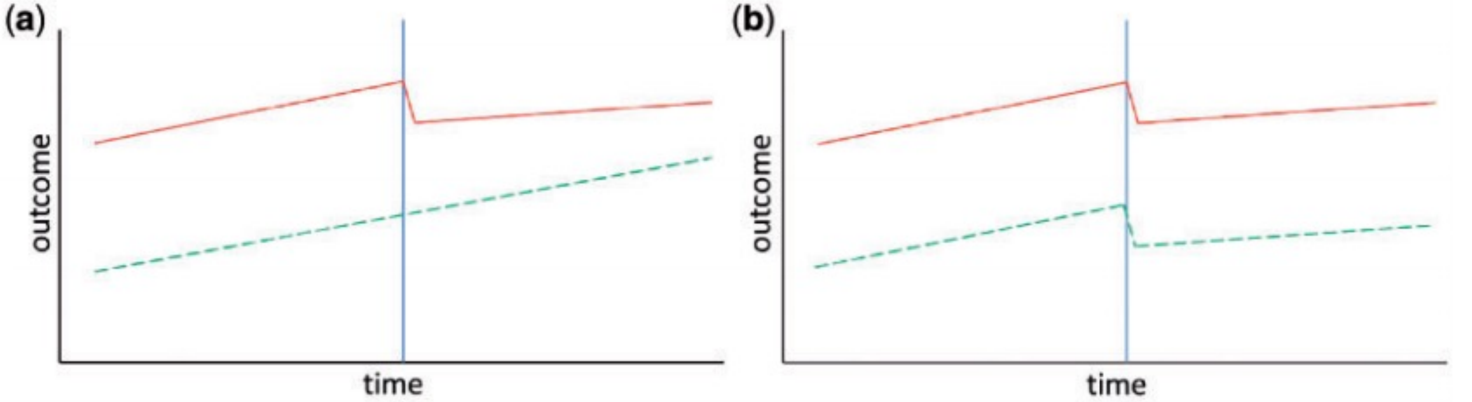


Figure 1. Controlled interrupted time series. Solid line = intervention series, dashed line = control series. (a) Here there is an effect in the intervention series (step and slope decrease) but no effect in the control series, which increases confidence that the effect is due to the intervention. (b) Here there is a step and slope decrease in both the intervention and control series, suggesting the change is due to some other event or co-intervention that affected both groups.

Source: Lopez Bernal et al. *Int J Epidemiol* 2018;0(0):1-12.

Examples of negative control series

- Same outcome in different (but similar) population not affected by intervention
- Different (but similar) outcome not affected by intervention in same population
- Same outcome in same population but in different time period

Exercise

Think of a negative control series for each of the three types above for the intervention of price increase on alcopops

Negative control series – example

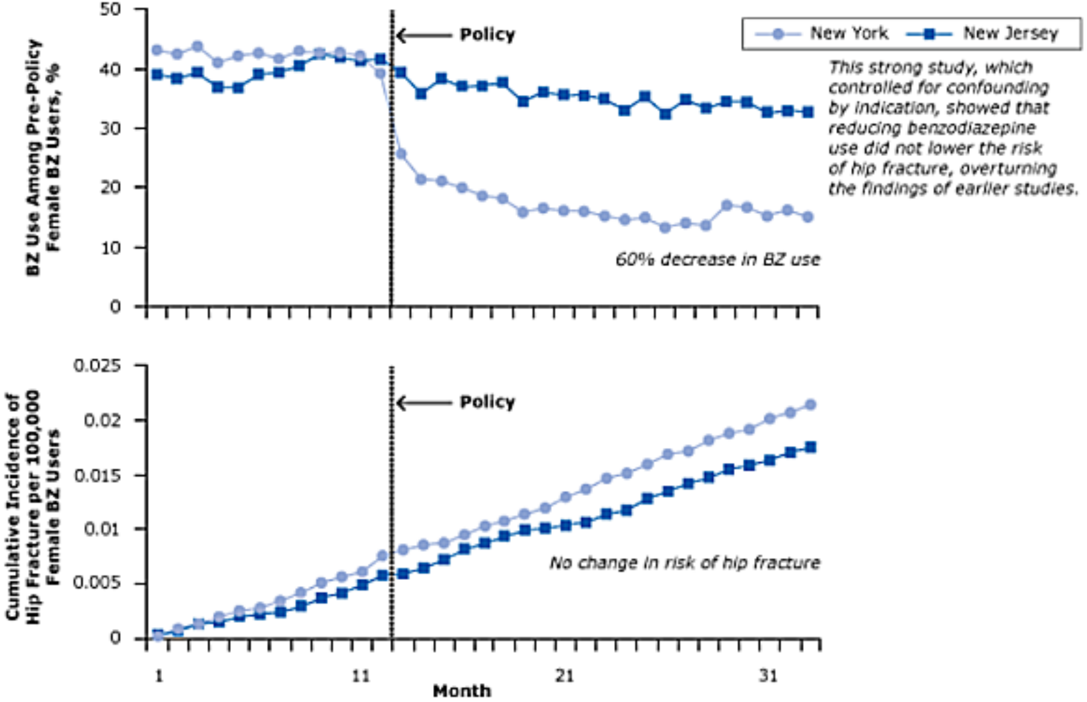


Figure. Example of negative control series. (Soumerai et al. 2015. *Prev Chronic Dis*)

Negative control series – example

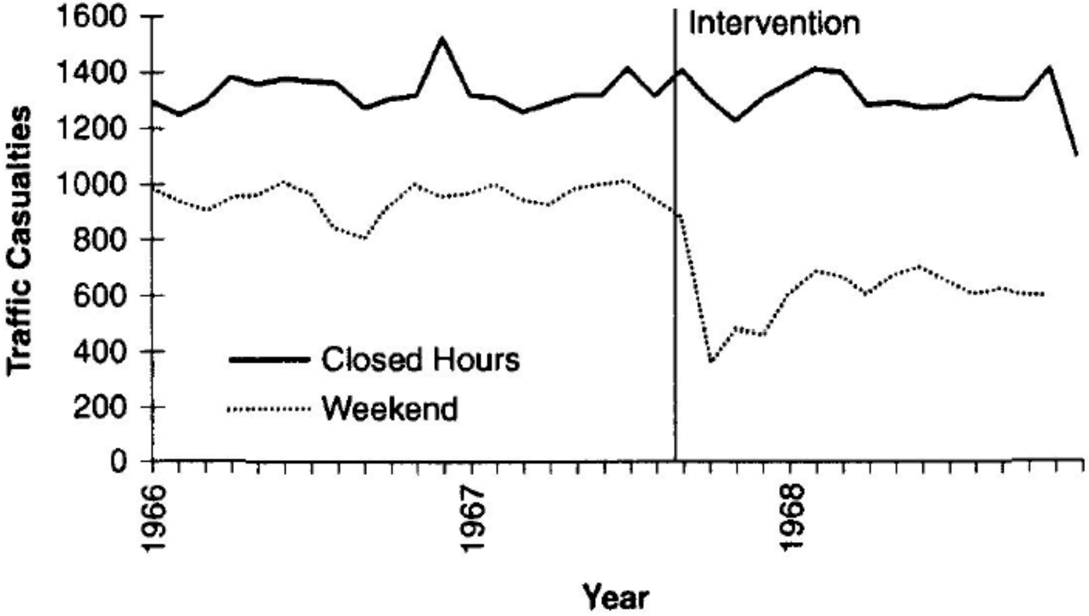


FIGURE 6.6 The effects of the British Breathalyzer crackdown on traffic casualties during weekend nights when pubs are open, compared with times when pubs were closed

Shadish, Cook, Campbell. Experimental and quasi-experimental designs for generalized causal inference. 2002

ABC Catalyst program claims high cholesterol does not cause heart disease.

- Two-part program claims high cholesterol does no cause heart disease…

- …and statins (cholesterol-reducing drugs) do not save lives

- Medical experts respond to say these claims are dangerous.

Watch this clip from Media Watch online here

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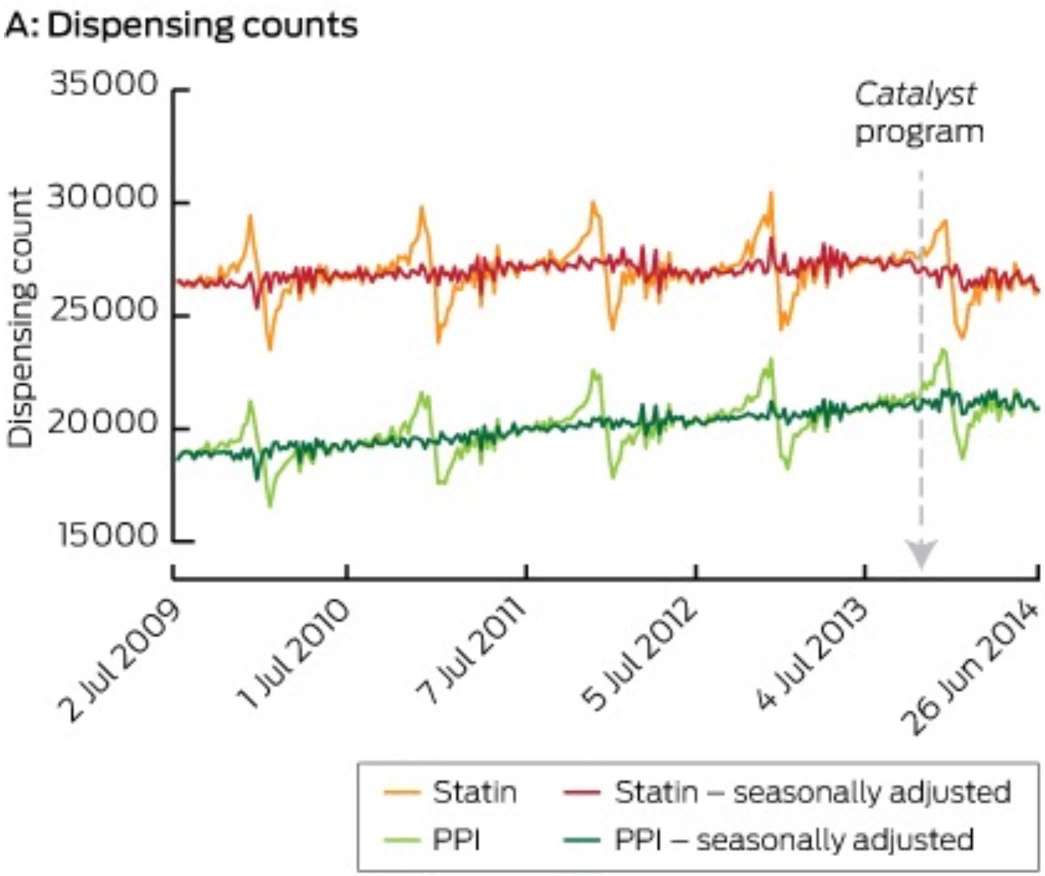
Negative control series – example



Schaffer et al. MJA 2015;202(11):591.

Undertaking ITS analysis

We will discuss two modelling approaches

1. Segmented regression

2. ARIMA models

Segmented regression modelling

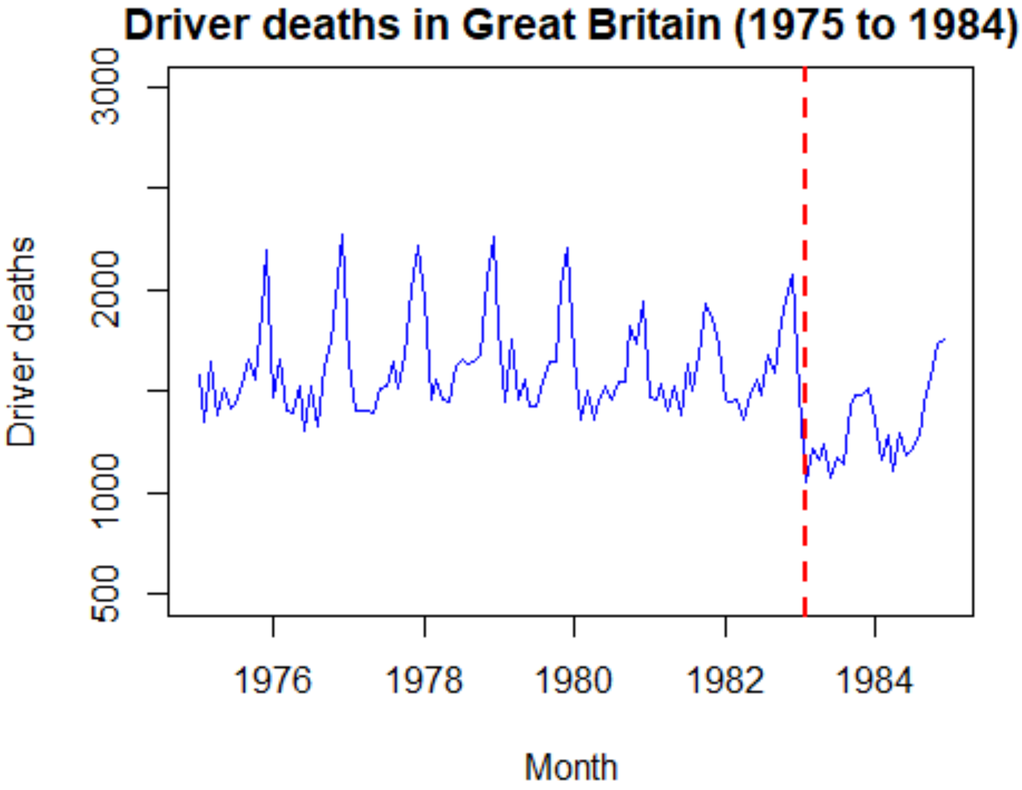
Step 1: Visualise your data

The first step is always to visualise your series using one or more of a time series line graph, seasonal plots, and decomposition plots.

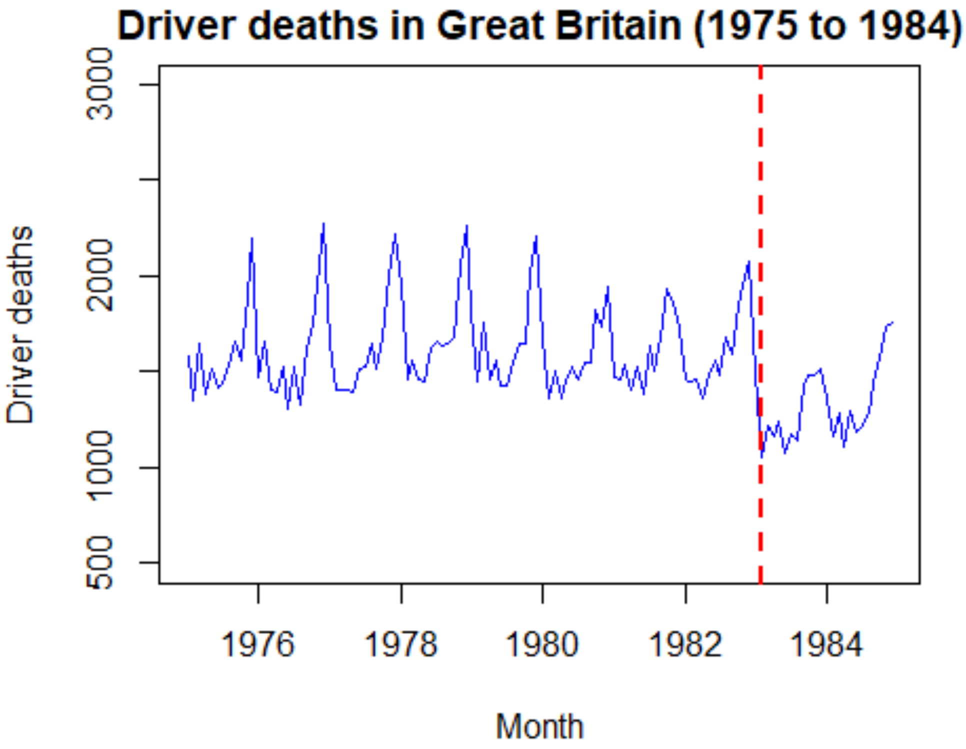
Some questions to ask when visualising your data:

- What is the potential shape of the intervention?
- Is the impact delayed?
- Is there a trend in the data?
- Will we need to adjust for seasonality?
- Are there any potential extreme or outlier data points that warrant further investigation?

Introduction of seatbelt law in Great Britain in March 1983



Step 2: If data have non-constant variance, apply log transformation



Pre-intervention

	time	step	ramp	pulse
1	1	0	0	0
2	2	0	0	0
3	3	0	0	0
4	4	0	0	0
5	5	0	0	0
6	6	0	0	0
7	7	0	0	0
8	8	0	0	0
9	9	0	0	0
10	10	1	1	1
11	11	1	2	0
12	12	1	3	0
13	13	1	4	0
14	14	1	5	0
15	15	1	6	0
16	16	1	7	0
17	17	1	8	0

Post-intervention

Step 3: Create necessary variables

For a segmented linear regression, you will typically need variables representing the following:

- Time since start of study (time)
- Intervention (step change)
- Time since intervention (slope change or ramp)

If necessary:

- Pulse change
- Seasonal dummy variables

```
seasonaldummy(data.ts)
```

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Step 3: Create necessary variables

Consider also:

1. Could the intervention impact be delayed/lagged? If so by how much?
2. Could a change in the outcome have changed prior to the intervention date?

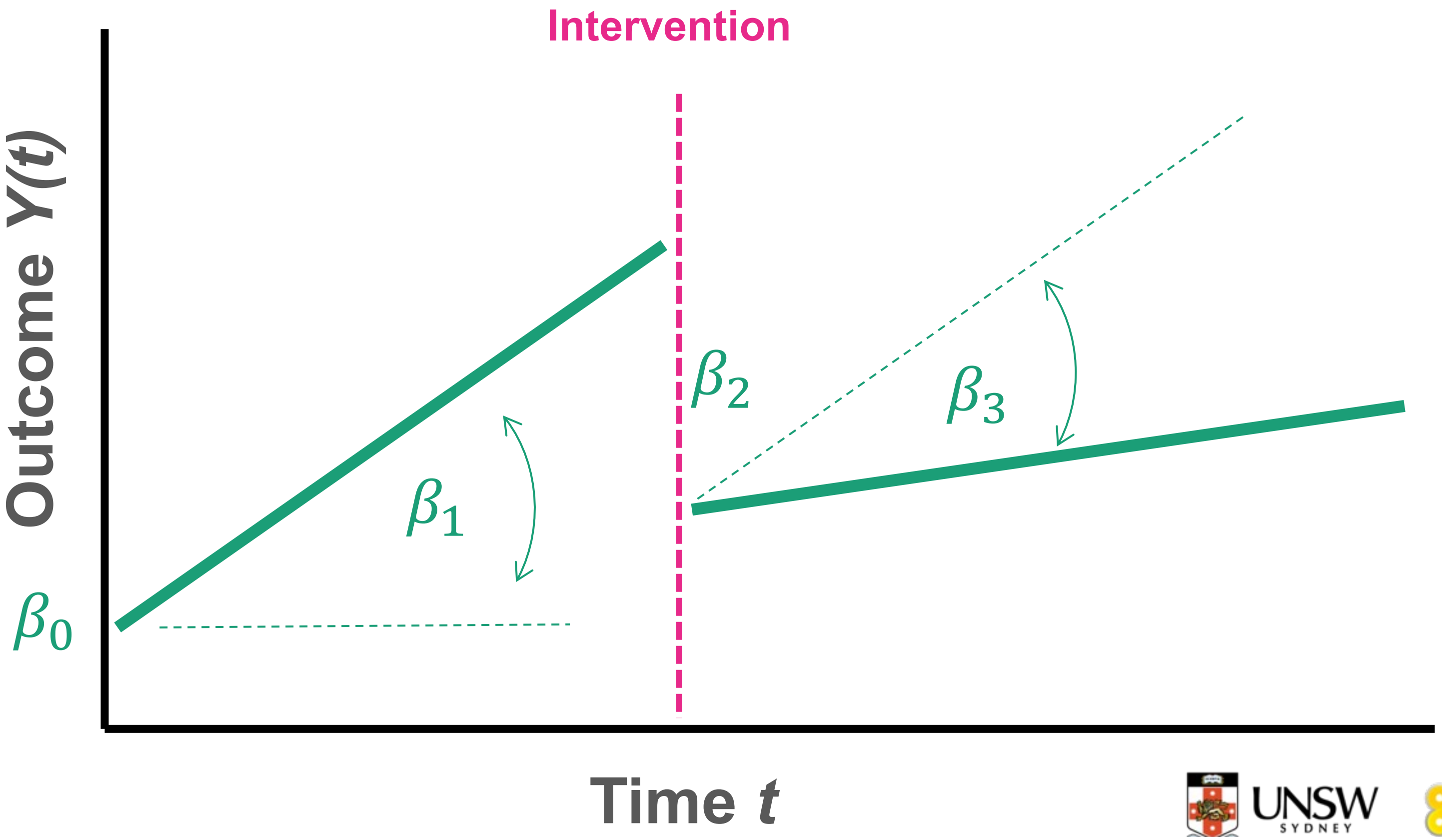
If so, adjust your variables as necessary.

Step 4: Estimate model

$$Y_t = \beta_0 + \beta_1 \times time\ since\ start\ of\ study + \beta_2 \times intervention + \beta_3 \times time\ since\ intervention + \epsilon_t$$

Parameter	Interpretation
β_0 = intercept	Value of Y_t at time 0 (typically not meaningful)
β_1 = baseline slope	Change in Y_t for a one unit increase in time
β_2 = step change post-intervention	Immediate level shift in Y_t post-intervention
β_3 = change in the baseline slope post-intervention	Change in pre-intervention slope of Y_t post-intervention

Step 4: Estimate model – visualising parameters



Step 4: Estimating model in R

1. Run model, including variables representing impact of intervention and to control for trend/seasonality

```
UKDD.model1 <- lm(UKDD ~ UKDD.time + belt + belt.after + UKDD.mon)
```

2. Check for residual autocorrelation

```
Box.test(UKDD.model1$residuals, lag = 12, type = "Ljung-Box")
```

3. Plot residuals to check model fit

```
plot(model1)
```

Step 5: Check residuals of model

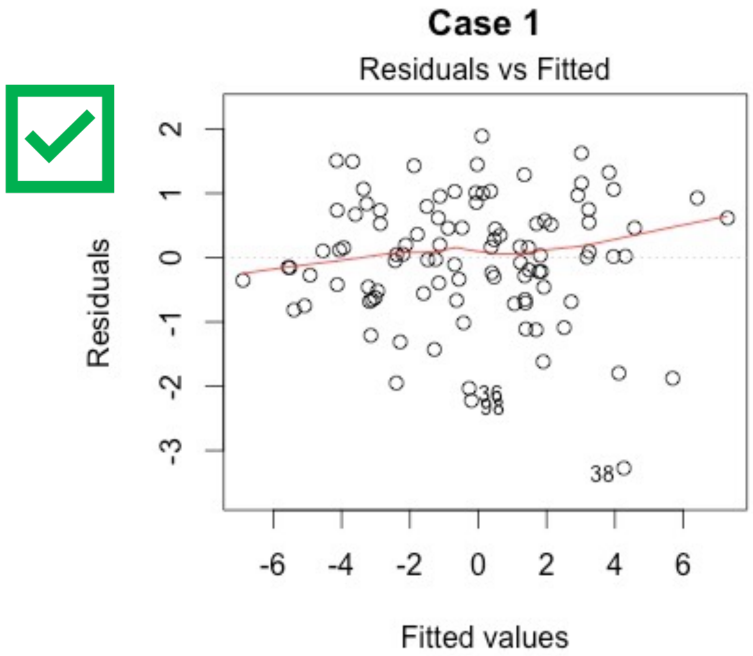
Use Ljung-Box test to check for residual autocorrelation – a p-value <0.05 indicates significant autocorrelation.

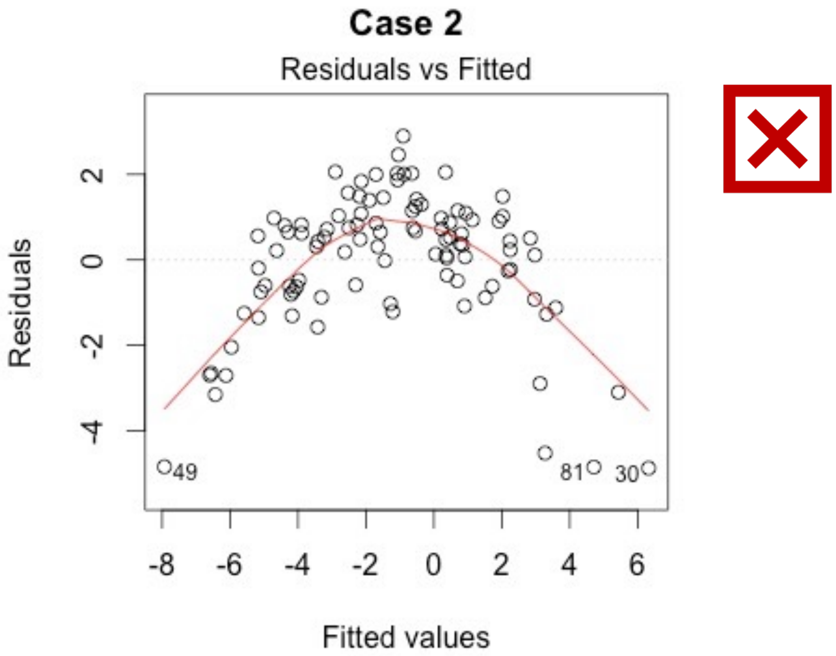
```
        Box-Ljung test

data:  UKDD.model1$residuals
X-squared = 11.637, df = 12, p-value = 0.4753
```

If your model isn't a good fit....

- Try transforming your outcome (if you haven't already)
- You may not have adequately controlled for seasonality
- You may have extreme values that have a large influence on results
- If there is significant residual autocorrelation – you may have to consider an AR or ARIMA model

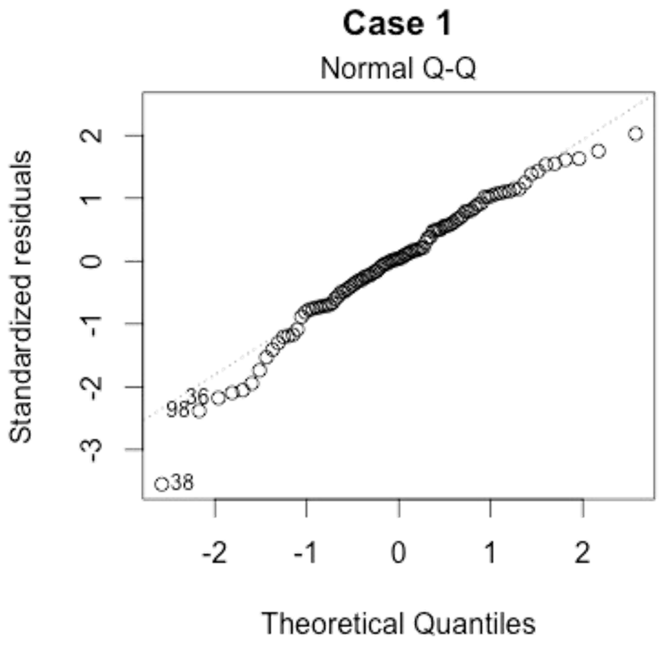
Step 5: Check residuals of model

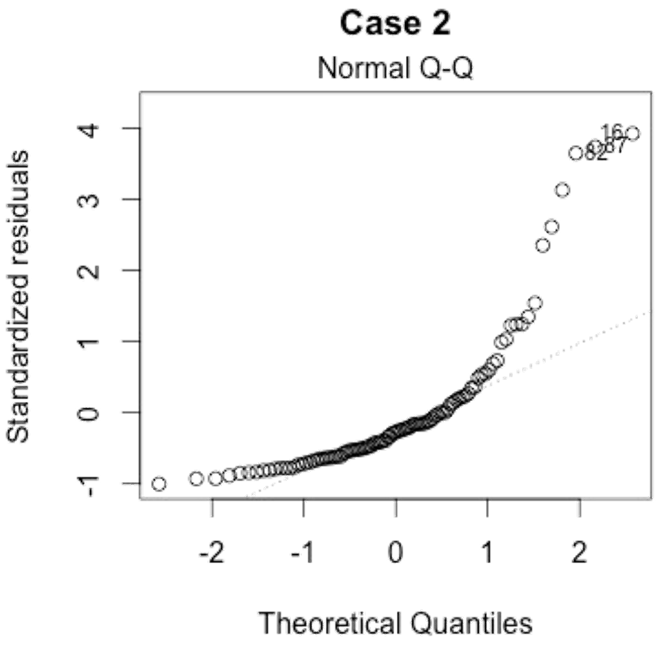




https://data.library.virginia.edu/diagnostic-plots/

Step 5: Check residuals of model





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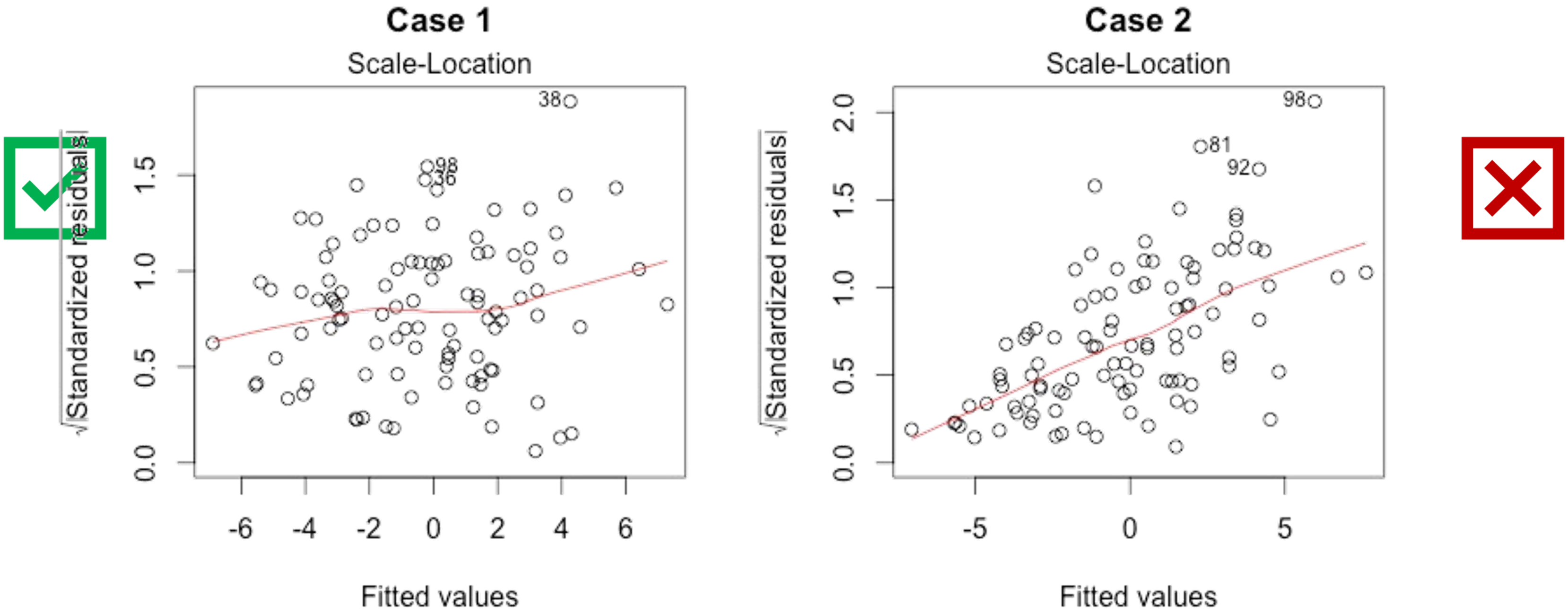
Step 5: Check residuals of model



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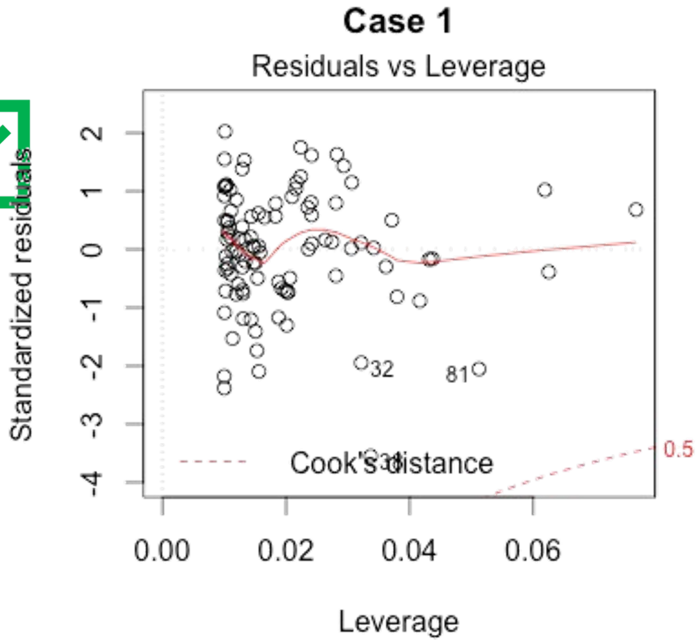
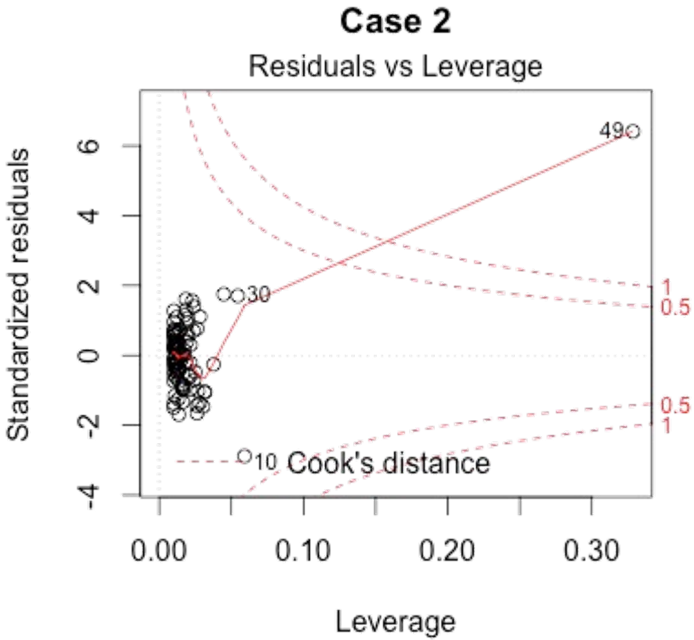
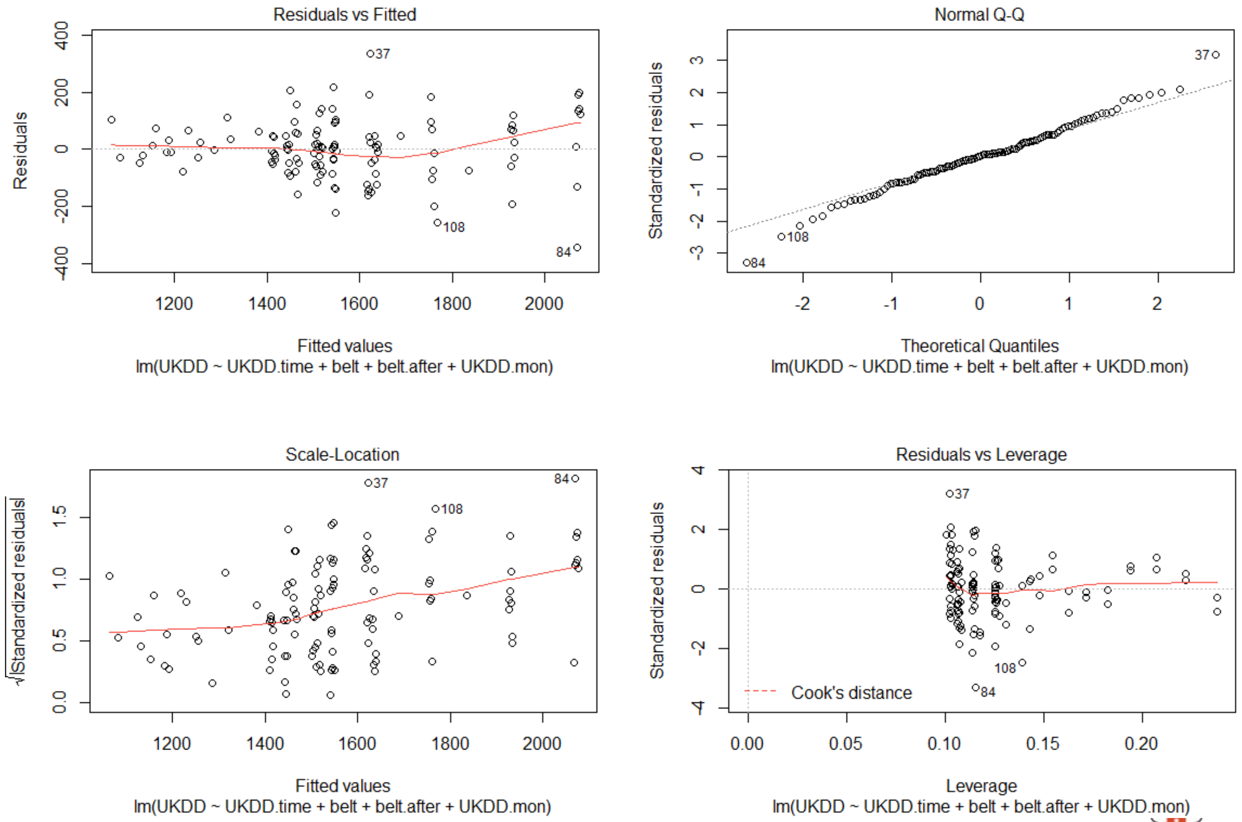
Step 5: Check residuals of model





https://data.library.virginia.edu/diagnostic-plots/

Step 5: Checks residuals of model



Step 6: Interpret results and write conclusion

$$Y_t = \beta_0 + \beta_1 \times time + \beta_2 \times intervention + \beta_3 \times time\ since\ intervention + \beta_4 Jan_t + \beta_5 Feb_t + \beta_6 Mar_t + \beta_7 Apr_t + \beta_8 May_t + \beta_9 Jun_t + \beta_{10} Jul_t + \beta_{11} Aug_t + \beta_{12} Sep_t + \beta_{13} Oct_t + \beta_{14} Nov_t + \epsilon_t$$

Estimate	Meaning	Interpretation
β_0	Outcome at time zero	***Typically not meaningful***
β_1	Change in outcome for every 1 time unit increase	Prior to the intervention, the outcome was (increasing/decreasing) by β_1 for each time unit
β_2	Immediate, sustained shift in the time series post-intervention	The intervention was associated with an immediate, sustained (increase/decrease) in the outcome of β_2
β_3	Change in pre-intervention slope	The intervention was associated with an (increase/decrease) in the pre-intervention slope by β_3; the new slope is $\beta_1 + \beta_3$
$\beta_4 - \beta_{14}$	Relative value of outcome compared with reference seasonal unit (in previous example December)	The outcome was β_4 (higher/lower) in a given month compared with the reference month ***Typically not necessary to interpret unless it is of particular interest***

Step 6: Interpret results and write conclusion

```
> broom::tidy(UKDD.model1, conf.int=TRUE)
# A tibble: 15 x 7
  term         estimate std.error statistic  p.value conf.low conf.high
  <chr>           <dbl>     <dbl>     <dbl>    <dbl>    <dbl>     <dbl>
1 (Intercept) 2077.        41.4       50.2  3.25e-75 1995.     2159.
2 UKDD.time     -0.0965     0.402     -0.240 8.11e- 1   -0.893     0.701
3 belt        -363.        53.6       -6.77 7.62e-10 -469.      -257.
4 belt.after     5.78       3.56       1.62 1.08e- 1   -1.28     12.8
```

In the 10 years prior to the introduction of the seatbelt law in March 1983, the number of driver deaths per month was constant with a baseline slope of -0.1 (95% CI -0.9 to 0.7). After introduction of the law, there was an immediate decrease in driver deaths of 363 (95% CI -469 to -257) that was sustained until the end of 1984. There was no change in the monthly slope (6, 95% CI -1 to 13).

What if your outcome is log transformed??

See: https://stats.idre.ucla.edu/other/mult-pkg/faq/general/faqhow-do-i-interpret-a-regression-model-when-some-variables-are-log-transformed/

$$\% \, change = (\exp(\beta) - 1) * 100$$

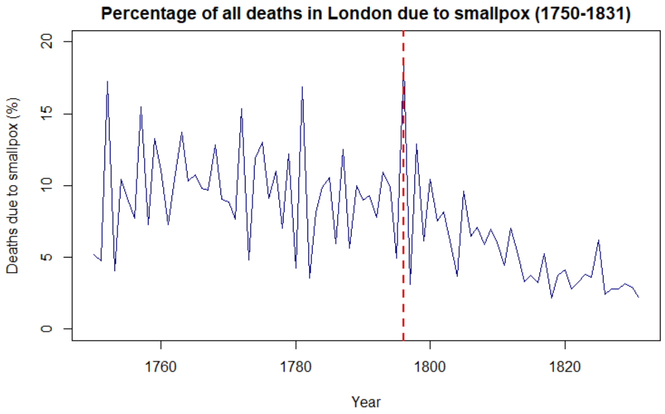
Smallpox deaths in London:

Change in slope (β) = -0.04167

Back transformed change in slope =

$$(\exp(-0.04167) - 1) * 100 \; = \; -3.3\%$$

After the smallpox vaccine was introduced, the rate of smallpox deaths was decreasing by 3.3% per year (95% CI -4.1% to -2.5%).



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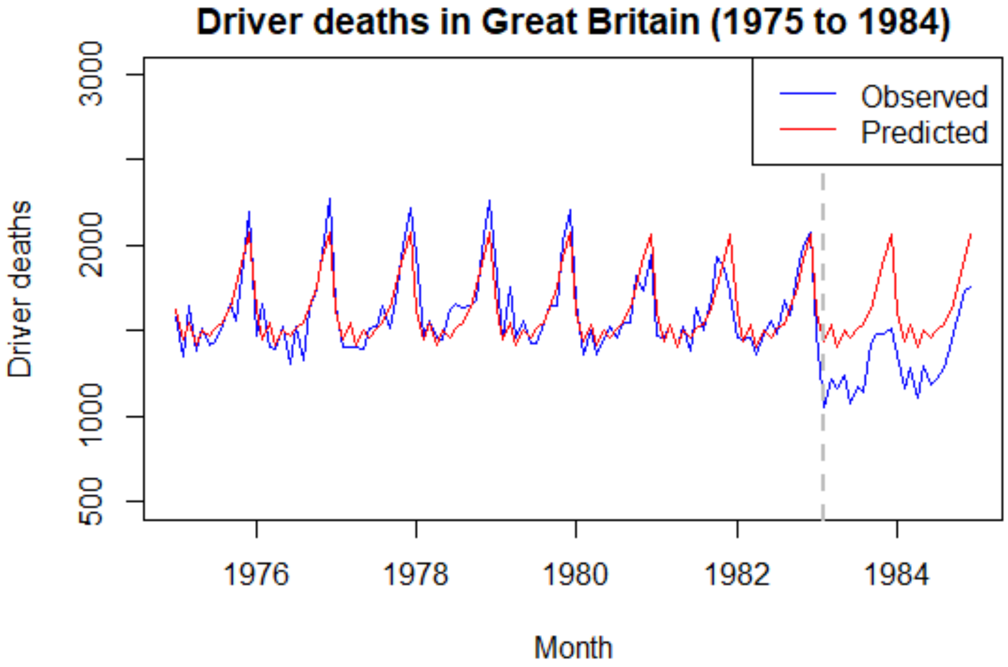
Step 7: Visualise your results (plot counterfactual)



Do your estimates make sense???

See also: Turner et al. Creating effective interrupted time series graphs: Review and recommendations. *Research Synthesis Methods* https://doi.org/10.1002/jrsm.1435

AR and ARIMA modelling

What is an ARIMA model?

A R I M A

Autoregressive

Integration
(differencing)

Moving average

ARIMA notation

$$ARIMA(p, d, q)$$

p = the order of the AR part of the model;

d = the differencing needed to eliminate trend (almost always 0 or 1);

q = the order of the MA part of the model;

p, d, q, are all integers, and can also be zero.

$$Y_t = c + \phi_1 Y_{t-1} + \phi_2 Y_{t-2} + \cdots + \phi_p Y_{t-p} + \epsilon_t$$

p is the order of the autoregressive component

$$Y_t = c + \epsilon_t + \theta_1 \epsilon_{t-1} + \theta_2 \epsilon_{t-2} + \cdots + \theta_q \epsilon_{t-q}$$

q is the order of the moving average component

ARIMA notation

A seasonal ARIMA model is indicated by:

$$ARIMA(p,d,q)\times(P,D,Q)$$

Where P and Q are the autoregressive and moving average orders for the seasonal component, and D is the degree of seasonal differencing (almost always 0 or 1).

If $d = 1$ and your data are seasonal, then D will almost always be 1 as well.

ITS analysis with ARIMA modelling

Trend is dealt with by differencing (not by inclusion of a time covariate)

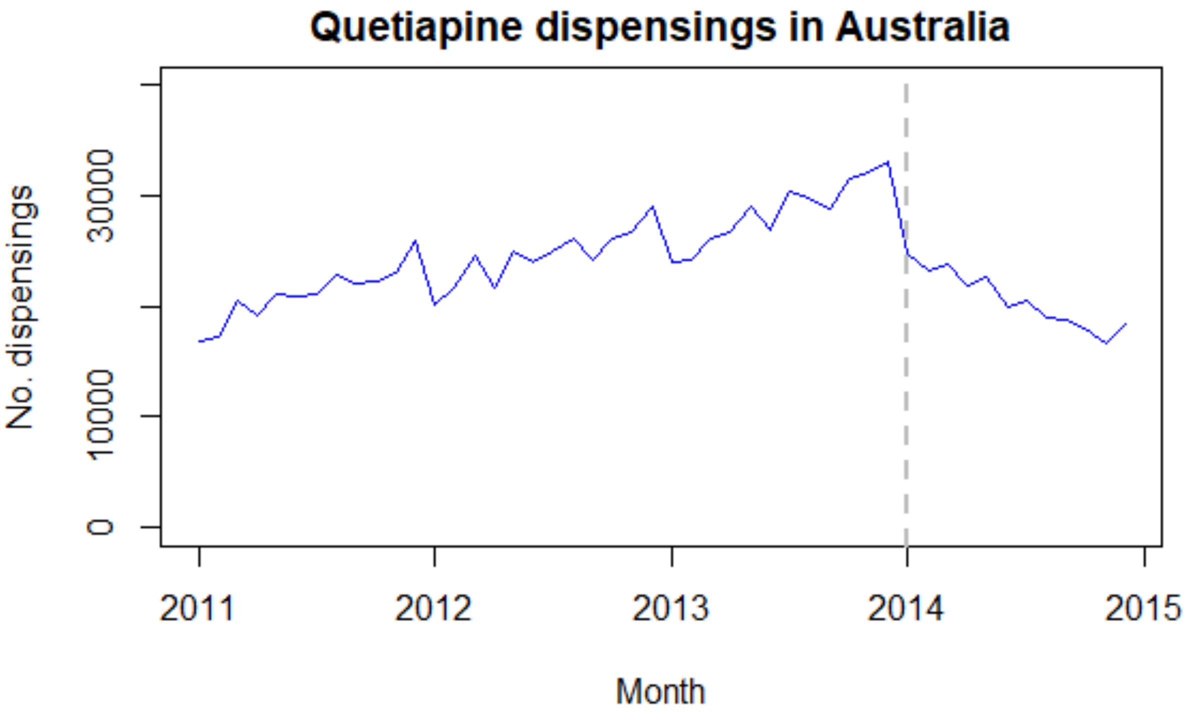
Seasonality is dealt with by differencing (not by seasonal dummy variables)

```
model2 <- auto.arima(data.ts, d=1, D=1, seasonal=c("TRUE","FALSE"),
                     xreg=cbind(step, time.after))
```

Include external regressors to estimate change in level (step change) and change in slope

*Note: with a full ARIMA model, you cannot easily estimate the pre-intervention trend

Example: quetiapine dispensing after increased restrictions on its prescribing



What is the potential shape of the intervention?

Do you expect there to be seasonality?

Is there a trend?

Explore model order with *auto.arima* | Fit model with *sarima*

Due to trend, d=1

Due to seasonality
and since d=1, D=1

```
auto.arima(quet, d=1, D=1, xreg=cbind(quet.step, quet.ramp),
           seasonal=TRUE, stepwise=FALSE)
```

```
quet.model1 <- sarima(quet, p=2, d=1, q=0, P=0, D=1, Q=1, S=12,
                      xreg=cbind(quet.step, quet.ramp))
# Estimates
quet.model1$ttable
# Confidence intervals
confint(quet.model1$fit)
```

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Interpreting results – ARIMA

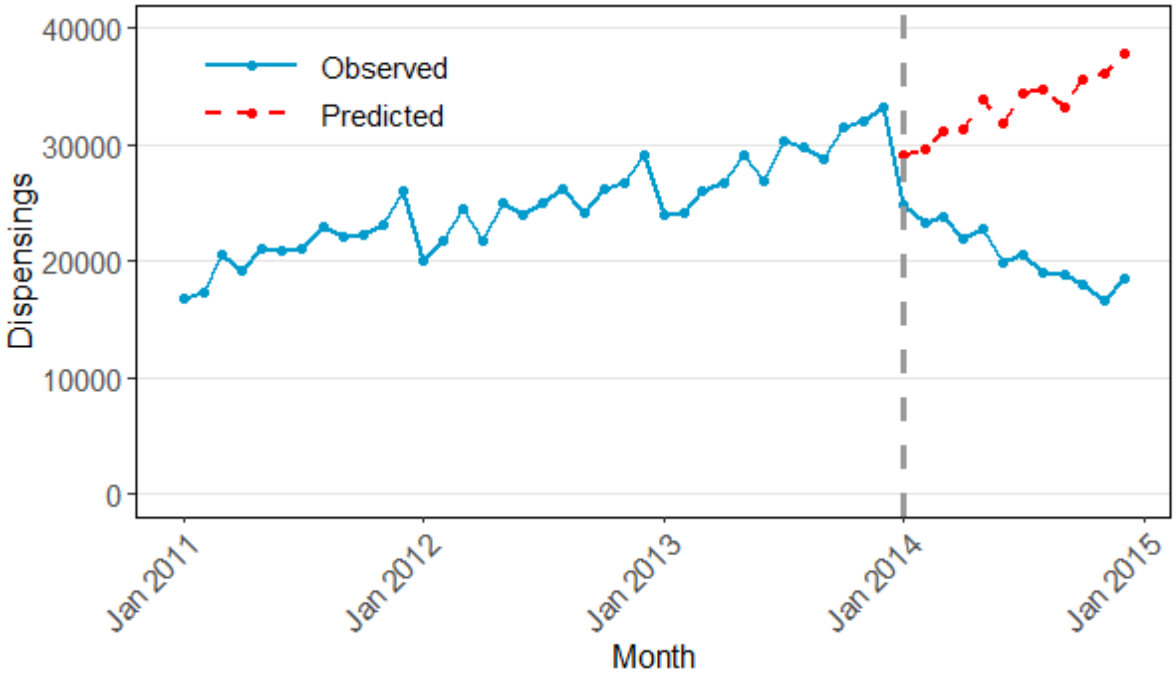
```
> sarima(quet, p=2, d=1, q=0, P=0, D=1, Q=1, S=12,
+                 xreg=cbind(quet.step, quet.ramp))

$ttable
            Estimate       SE   t.value p.value
ar1          -0.8730   0.1240   -7.0427  0.0000
ar2          -0.6731   0.1259   -5.3480  0.0000
sma1         -0.6069   0.3872   -1.5674  0.1275
quet.step -3284.7792 602.3365   -5.4534  0.0000
quet.ramp -1396.6523 106.6329  -13.0978  0.0000

$AIC
[1] 12.62811

$AICc
[1] 12.66072

$BIC
[1] 12.83098
```

quet.step = before or after intervention

quet.ramp = time since intervention

```
> confint(sarima(quet, p=2, d=1, q=0, P=0, D=1, Q=1, S=12,
 xreg=cbind(quet.step, quet.ramp))$fit)
                   2.5 %        97.5 %
 ar1           -1.1159676    -0.6300560
 ar2           -0.9198344    -0.4264428
 sma1          -1.3658856     0.1520087
 quet.step  -4465.3371060 -2104.2212517
 quet.ramp  -1605.6489999 -1187.6555303
```

Plot counterfactual



Segmented regression or ARIMA??

	Segmented regression (SR)	ARIMA (including AR models)
Data distribution	Normal (continuous outcome) Poisson (count outcome)	Normal (continuous outcome)
Trends	Simple, regular trends only (e.g. linear)	Complex trends
Seasonality	Simple seasonality via dummy variables	Complex seasonality
Autocorrelation	For simple autocorrelation, accounting for trends and seasonality may remove it	Complex autocorrelation
Implementation	Simple	Can be challenging to find the most appropriate *p*, *q*, *P*, and *Q* terms
Baseline slope	Can be estimated	AR model – can be estimated ARIMA model – cannot be estimated
R functions	`lm()` or `glm()`	`auto.arima()` in `forecast` package `sarima()` in `astsa` package

Final words

Interrupted time series analysis is a powerful approach to evaluate the impact of large-scale interventions, especially when combined with control series

To ensure robust results, any modelling approach should take into account trends, seasonality, and autocorrelation

Simpler is (usually) better—sometimes a simple linear regression is all you need!

As with most observational studies, be wary of inferring causal relationships